REMARKS/ARGUMENTS

Applicant uses the paragraph numbering of the office action in responding to the Examiner's remarks.

Appeal Brief

¶¶1-2. It is noted that applicants filed a notice of appeal but not an appeal brief. It is further noted that although the rejections are characterized as "new" at least some were made in the first office action to which applicants responded. By making rejections in the first office action, withdrawing them in the second office action, and then reinstating the rejections in the third office action in the form of "new rejections," the Examiner has not yet commented on applicant's rebuttal of the rejections made in response to the office action. Applicant files this paper under 37 C.F.R. §1.111 to avoid abandonment of this application.

Information Disclosure Statement

¶6. As per the Examiner's invitation, page two of the PTO/SB/08A filed May 11, 2003 is submitted herewith.

Withdrawn Rejections

¶¶7-9. Applicant notes that the rejections under 102(b) and 102(e) as being allegedly anticipated by Prusiner have been withdrawn.

Provisional Obviousness Type Double Patenting Rejections

¶¶10-11. Claims 11, 14, 15, 16, 19, and 21-25 of the instant application are provisionally rejected for alleged obviousness type double patenting over claims 11-25 of Application No. 09/724,575. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited case provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election

of species, and the claims in the cited case are in conflict with those in the present case at this time.

Rejections Under 112, First Paragraph

¶¶12-29. Due to the length of this rejection, each paragraph will be considered in turn.

¶¶12-13. These paragraphs summarize the claims being rejected. No response is needed.

¶14. The Examiner alleges that the PDAPP mouse model does not exhibit Alzheimer's disease, Down's syndrome or other amyloidogenic disease as it occurs in humans as evidenced by Schenk, or Games. Insofar as the Examiner is suggesting that the PDAPP mouse model is not a good model of Alzheimer's disease or Down's syndrome in humans, Applicant disagrees.

The Schenk and Games references contradict rather than support the Examiner's allegations of inadequacy of the PDAPP mouse model. As noted above, Games appeared as the cover story of Nature and describes many characteristics of the PDAPP mouse that closely resemble the pathology in Alzheimer's disease. The reference concludes:

> A most notable feature of these transgenic mice is their Alzheimer-like neuropathology . . . . Our transgenic model . . . offers a means to test whether compounds that lower Aβ production and/or reduce its neurotoxicity in vitro can produce beneficial effects in an animal model prior to advancing such drugs into human clinical trials.
>
> *See* p. 527, first column, second paragraph.

Similarly, Schenk, which also formed the cover story of the edition of Nature (*see* Schenk *et al.*, *Nature*, 400:173-177 (1999)) in which it appeared, concludes:

> To our knowledge, this is the first report of a clinically relevant treatment that reduces the progression of AD-like neuropathology in a transgenic model [the PDAPP mouse] of the disease. . . . Collectively, the results suggest that amyloid-β immunization may prove beneficial for both the treatment and prevention of Alzheimer's disease.
>
> *See* p. 177, paragraph bridging cols. 1 and 2.

Thus, the Games and Schenk references support rather than contradict the view that the PDAPP mouse does exhibit many of the pathological characteristics of Alzheimer's disease, and is regarded in the art as a model reasonably predictive of results in humans.

The validity of the PDAPP mouse as a model system for predicting effects of Aβ in humans is further confirmed by the performance of human clinical trials. The Investigational New Drug Application ("INDA") supporting the clinical trials was based on essentially the same data as is contained in the present application. That the FDA allowed clinical trials to occur shows that it considered the preclinical evidence, including the results in PDAPP mouse, as being reasonably predictive of success in humans.

¶15. The Examiner alleges that administration of Aβ42 to Alzheimer's patients is not predictive of how administration of PrP or AScr affects patients with prion-related diseases. The Examiner alleges that there are no working examples relating to treatment of such diseases. In response, applicant has previously made of record two publications dated after the priority date of the present invention showing that active immunization with PrP and passive administration of antibodies to PrP in a mouse model of prion disorder produces results similar to those described for immunization of Aβ (*see* Sigurdsson *et al.*, *Am. J. Pathol.*, 161, 13-17 (2002) (active); Sigurdsson *et al.*, *Neuroscience Letters*, 336, 185-187 (2003) (passive)). The authors acknowledge that their report represents an extension of previous work relating to Aβ immunization (*see Am. J. Pathol.* at p. 15, second column, first paragraph). The similarity of results for immunization with PrP and Aβ42 in mouse models of prion and Alzheimer's disease respectively indicates that administration of Aβ to Alzheimer's disease is predictive of how administration of PrP or AScr affects patients with prion-related disease.

¶16. The Examiner alleges that the specification does not provide any guidance or examples that would enable an artisan to make formulations containing prion proteins or to determine signs and symptoms of prion disorders to correlate with treatment. In response, the Examiner's has not addressed the considerable guidance provided by the specification at pp. 53-59 with respect to preparation of formulations for any amyloidogenic peptide, include PrP and AScr. A "specification disclosure which contains a teaching of the manner and process of

AScr. A "specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi,* 169 USPQ 367, 369 (CCPA 1971) (emphasis in original). Here, the Examiner has not met his burden of explaining why undue experimentation would be required to combine a prion protein with an adjuvant. With respect to sign and symptoms, it is noted that the present claims do not contain a monitoring step to detect such signs and symptoms. In any event, it is submitted that the signs and symptoms of prion-based diseases were well known in the medical field at the priority date of the invention (see, *e.g.*, Goldfarb reference cited by the Examiner) and do not require repetition in the application.

¶17. The Examiner alleges that predicting the efficacy of using a possibly toxic protein based solely on the performance of a different protein is highly problematic. Applicant reiterates that the efficacy of prion proteins is not based solely on the performance of a different protein. As noted above, tests of the PrP in a mouse model of prion-based disease have shown similar results to test of Aβ in a mouse model of Alzheimer's disease. Moreover, although PrP and Aβ are different proteins, they both form remarkably similar amyloid fibrils are remarkably similar (*see* Sunde *et al.*, *J. Mol. Biol.*, 273:729-739 (1997)). Fibrils formed from various amyloid proteins similar high-resolution X-ray fiber diffraction patterns, consistent with a helical array of beta-sheets parallel to the fiber long axis, with the strands perpendicular to this axis irrespective of the nature of their precursor proteins (*Ibid*). Thus, it is not unreasonable to infer that treatment of prion-based disease with PrP or AScr plus adjuvant from treatment of Alzheimer's disease with Aβ. The results from tests in animal models of prion disease confirm the reasonableness of this inference.

¶¶18-19. The Examiner refers to possible side-effects from inducing an immune response in the nervous system as a source of undue experimentation. It is respectfully submitted that

requiring a patent applicant to teach means for avoiding all side effects imposes too high a standard of enablement. Here, clinical trials have indicated that inflammatory side effects may result in a small number of patients (15 out of 360), as discussed in the Elan press releases (of record) , and Munch (of record). Moreover, in the few patients that might experience side effects, there is the possibility of mitigation by immunsuppressants (*see* Munch of record at p. 1085). Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Moreover, the requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Id.*

¶20. The Examiner notes that there are a number of distinct prion-based diseases that share the common element of a prion protein but are caused by different mutations or isoforms. The Examiner takes the view that undue experimentation would be required on how each individual isoform and mutation will affect the immune system of the patient.

As discussed above, the application discloses a general strategy in which pharmaceutical compositions comprising an agent and adjuvant generate an antibody response against an amyloid component and thus remove the amyloid component or reduce its further accumulation in amyloid deposits in a subject. This strategy accommodates different amyloidogenic diseases characterized by different amyloid components by appropriate selection of the agent in the composition. For example, to treat Alzheimer's disease, one can select an agent that generates an antibody response to Aβ, and to treat prion-based disease, one can select an agent that generates an antibody response to the prion component of the disease. Insofar as different prion-based diseases are characterized by different mutations or isoforms of prion protein, the different subtypes of disease can similarly be accommodated, if necessary, by selection of an agent that induces antibodies to the prion form present in the appropriate subtype. Mutagenic or isoform variation between different forms of prion-based disease does not,

however, necessarily imply that a different agent is needed for treatment of each disease subtype. Although a particular mutation in a prion may be critically affect the path of disease, it is less likely to change substantially the immunoreactivity of the fragment. Thus, many antibodies against one form of prion protein are likely to react with other form notwithstanding mutagenic or isoform variation. For example, the antibodies shown to have pharmacological activity against prion-based disease by Sigurdsson *et al.*, *Neuroscience Letters,* 336, 185-187 (2003) were all raised against normal PrP rather than the pathogenic form, AScr. For these reasons, it is submitted that general strategy for design of pharmaceutical compositions can accommodate variations between prion protein in different types of prion-based disease.

¶21. The Examiner alleges additional unpredictability with respect to mutants, fragments, and peptides. The Examiner also says that for small peptides, conjugation appears to be required for promoting an effective immune response. In response, it is noted that the recitation of mutants, fragments and peptides occurred with respect to the description of a precursor protein in claim 13. Claim 13 has been cancelled in a previous response. Claim 11 does including variants of PrP or AScr associated with hereditary amyloidosis. However, these are not random mutations, which may have the unpredictable effects, but rather natural mutations known to associated with amyloidogenic disease. There is no reason to think that immune responses directed to components derived from precursor proteins having such mutations would be less effective in treating prion disorders than immune responses directed to components from a wildtype precursor protein. With respect to the Examiner's comments on small peptides, it is noted that the claims as presently formulated are directed to PrP and AScr, which are not small peptides.

¶22. The Examiner cites Hsiao as teaching that Alzheimer's disease and prion disease differ in their location of their pathogenesis and the proteins which lead to the respective diseases. This raises essentially the same issue discussed in paragraph 15 above, and applicant responds in the same way.

¶23. The Examiner cites Goldsby as teaching that active immunization is not predictable as peptides are not generally immunogenic. In fact, Goldsby does not say that

peptides are not generally immunogenic but only that they are not *as* immunogenic as proteins (p. 461, second column, first paragraph). In any event, as noted above, the present claims are directed to use of PrP or AScr, which are proteins.

¶24. The Examiner cites Smith and Weissman as suggesting that prion acquired disorders can be acquired by consumption or administration of a prior precursor protein. However, these references do not disclose administration of prion protein with an adjuvant, and as such are outside the scope of the claims as presently formulated.

¶25. The Examiner cites Diomede as discussing possible toxicities of prion protein to certain types of cells *in vitro*. In response, it is submitted that the relevance, if any, of these in vitro observations to in vivo administration is speculation. In any event, Applicant reiterates that enablement of the present methods does not require freedom from all side effects.

¶26. The Examiner cites Harmey as teaching that immunization of mice with 16 synthetic peptides derived from PrP yields monoclonal antibodies which vary in their specificity, strength of binding and Ig class, from which the Examiner alleges undue experimentation would be required to achieve the desired effects. It is reiterated that the present claims are directed to PrP and AScr. These proteins are expected to induce a range of different antibodies with epitopes at different places throughout the molecules. As shown by Sigurdsson, immunization with PrP is effective in inhibiting development of prion-based disease.

¶27. The Examiner repeats the allegation that results from Aβ are not predictive of similar results using PrP. This raises the same issue as paragraph (15) and applicant responds in the same way.

¶28. The Examiner alleges the specification does not enable prevention when only treatment is exemplified in the references herein. In response, it is noted that this rejection does not appear to take into account the amendment of the claims in the previous response, whereby the claims are directed to methods of treatment.

¶29. The Examiner concludes by stating that the rejection under 35 U.S.C. §112, first paragraph is maintained. No additional response is needed excepted to reiterate that many of the above grounds of rejection had in fact previously been withdrawn in the final office action, and were reinstated rather than "maintained" in the present office action.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Rosemarie L. Celli

Rosemarie L. Celli
Reg. No. 42,397

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 650-326-2422
RLC/aeb
60209987 v1